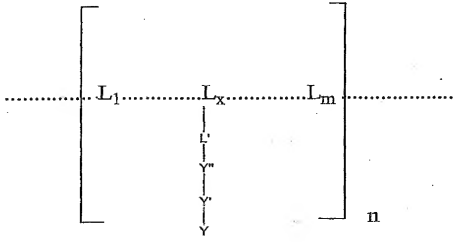
Amendments to the Claims

1. (Currently Amended) A method of preparing covalent antibodies or fragments thereof ~~that~~ that bind a peptide or protein covalently and catalytic antibodies or fragments thereof that ~~covalently bind to~~ and hydrolyze the peptide or protein, comprising:

producing in an organism, antibodies to a covalently reactive polypeptide antigen analogue ((pCRA) of formula (1):



(1)

Wherein, L_1 . . .Lx . . . Lm are components defining an antigenic determinant of the peptide or protein,

Lx is an amino acid residue,

L' is a side chain functional group of Lx,

Y" is or a linker,

Y' is an optional charged or neutral group,

Y is a covalently reactive electrophilic group ~~that reacts specifically with an antibody that binds to said antigenic determinant~~,

Optionally, Y", Y' or Y contains a water-binding group as a terminal or internal component;

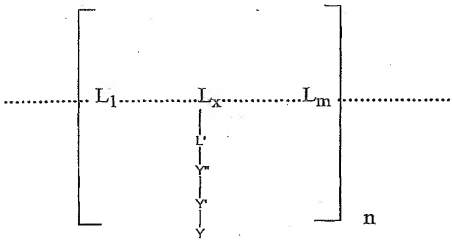
n is an integer from 1 to 1000; and

m is from 4 to 30;

screening and selecting for antibodies or antibody fragments thereof that covalently bind to the pCRA or to the peptide or protein having one or more of the antigenic determinants comprising the pCRA to identify covalent antibodies produced in the organism; and

screening and selecting for antibodies or antibody fragments thereof ~~that covalently bind to the pCRA and screening from among the covalently binding antibodies for antibodies that catalytically hydrolyze a peptide bond in~~ catalyze hydrolysis of one or more peptide bonds in the peptide or protein having ~~the~~ an antigenic determinant contained in ~~comprising~~ the pCRA to identify catalytic antibodies produced in the organism, thereby preparing covalent antibodies and catalytic antibodies.

2. (Withdrawn and currently amended) A water-binding, covalently reactive polypeptide antigen analogue (pCRAW) of formula (1) or pCRAW:



wherein, $L_1 \ldots Lx \ldots Lm$ are components defining an ~~a polypeptide~~ antigenic determinant of the polypeptide or protein,

Lx is an amino acid residue,

L' is a side chain functional group of Lx,

Y" is or a linker,

Y' is an optional charged or neutral group,

Y is a covalently reactive electrophilic group ~~that reacts specifically with an antibody that binds to said antigenic determinant~~,

Y", Y' or Y contains a water-binding group as a terminal or internal component;

n is an integer from 1 to 1000; and

m is from 4 to 30.

3. (Withdrawn) The pCRAW of claim 2, wherein the water-binding group is composed of a site that binds a metal ion which chelates one or more water molecules.

4. (Withdrawn) The pCRAW of claim 3, in which the metal is zinc, copper, nickel, cobalt, calcium or magnesium.

5. (Withdrawn) The pCRAW of claim 2, in which the metal binding group is selected from: -(His).sub.n- where n=2 or more, -Cys-X-Cys- or –Cys-X-CYS- wherein X is an amino acid residue, ethylene diamine tetraacetic acid or diaminomethyl pyridine.

6. (Currently Amended) The method of claim 1, wherein binding of the covalent ~~and catalytic~~ antibodies to the peptide or the protein is resistant to dissociation by a denaturant that disrupts non-covalent antigen binding.

7. (Currently Amended) The method of claim1, wherein the binding of the covalent ~~and catalytic~~ antibodies to the polypeptide or the protein is resistant to dissociation by 2% solium dodecyl sulfate.

8. (Previously Presented) The method of claim1, wherein the protein is HIV-1 gp120.

Claims 9-10 (Canceled)

11. (Previously Presented) The method of claim 1, wherein the covalent antibodies or catalytic antibodies are polyclonal antibodies identified in the serum of said organism.

12. (Previously Presented) The method of claim 1, wherein the antibodies are monoclonal antibodies or antibody fragments obtained from lymphocytes of said organism; wherein the stes of screening and selecting further comprise:

(a) preparing a library of hybridoma cell lines, virus-transformed cell lines or immunoglobulin fragment genes expressed from a vector prior to screening and selecting for the covalent antibodies and the catalytic antibodies or antibody fragments thereof; and

(b) purifying the covalent antibodies and catalytic antibodies or the antibody fragments thereof.

13. (Currently Amended) The method of claim 12, in which the antigenic determinant of the pCRA [(is)] comprises gp120, VIP, Factor VIII, epidermal growth factor receptor, CD4, ß-amyloid peptide 1-40, or ß-amyloid peptide 1-42 or peptide fragments thereof.

14. (Canceled).

15. (Previously Presented) The method of claim 12, wherein the organism is a transgenic mouse expressing human antibody genes.

16. (Original) The method of claim 12, wherein the organism is a mouse.

17. (Original) The method of claim 12 wherein the vector is selected from the group consisting of phage display vectors, retroviral display vectors, yeast display vectors, bacterial display vectors and mammalian display vectors.

18. (Previously presented) The method of claim 1, wherein the antibody fragments are single chain Fv fragments obtained by steps comprising:

a) preparation of the immunoglobulin VL and VH cDNA by reverse-transcriptase polymerase chain reaction;

b) cloning the VL and VH cDNA in a vector in a form enabling their expression as single chain Fv fragments expressed on the surface of a display vector; and

c) contacting the vector particles with immobilized pCRA of claim 1, removal of unbound vector particles by washing, and expression of the Fv genes from the pCRA-bound vector particles in soluble form in prokaryotic or eukaryotic cells.

19. (Original) The method of claim 12, wherein lymphocytes are obtained by steps comprising:

a) contacting the lymphocytes with a pCRA;

b) separating lymphocytes that are bound to the pCRA from lymphocytes that are not bound to the pCRA.

20. (Canceled).

21. (Original) The method of claim 1, wherein the antibodies belong to the IgG, lgM, lgD, lgA or lgE classes.

22. (Currently amended) The method of claim 1, wherein the ~~antibodies~~ antibody fragments are fragments of lgG, lgM, LgD, lgA or lgE.

23. (Original) The method of claim 1, wherein [L_1 . . . Lx . . . Lm] represents an antigenic determinant of a microbial protein.

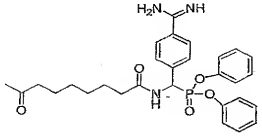
24. (Canceled).

25. (Original) The method of claim 1, wherein [L_1 . . . Lx . . . Lm] represents an antigenic determinant of a human, animal or plant protein.

Claims 26-28 (Canceled).

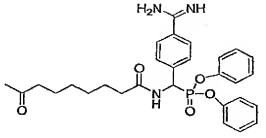
29. (Original) The method of claim 1, wherein n is from 1 to 23.

30. (Original) The method of claim 1, wherein the pCRA is gp120 derivatized at the Lys side chain amino groups at a density of 23 moles/mole protein with:

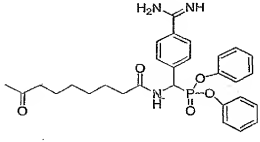


31. (Canceled).

32. (Original) The method of claim 1, wherein the pCRA is vasoactive intestinal peptide derivatized at the Lys20 side chain with



33. (Currently Amended) The method of claim 1, wherein the antigenic determinant of the pCRA is derived from the soluble extra-cellular domain of epidermal growth factor receptor, soluble extra-cellular domain CD4, Factor VIII, beta-amyloid peptide 1-40 or beta-amyloid peptide 1-42, each derivatized at Lys side chains with:



34. (Withdrawn and Currently Amended) The method of claim 12, wherein the monoclonal IgG ~~antibody~~ antibodies are clones YZ-18, YZ-20, and YZ-24 that catalyze the cleavage of gp120.

35. (Withdrawn and Currently Amended) The method of claim 12, wherein the monoclonal IgG ~~antibody~~ antibodies are clones YZ-18, YZ-19, YZ-20, YZ-21, YZ-22, YZ-23 and YZ-24 that bind the gp120-CRA of claim 30 and the binding is resistant to dissociation with 2% SDS.

36. (Withdrawn and Currently Amended) The method of claim 12, wherein the monoclonal IgG ~~antibody~~ antibodies are clones YZ-18, YZ-19, YZ-20, YZ-21, YZ-22, YZ-23 and YZ-24 that bind the gp120 and the binding is resistant to dissociation with 2% SDS.

37. (Withdrawn and Previously Presented) The method of claim 12, wherein full-length IgG, IgM and IgA antibodies are prepared from the antibody fragments by steps comprising:

a) insertion of the VL and VH domain cDNA at the 5' side of Ig constant domains contained in an expression vector by nucleic acid digestion and ligation procedures.

b) growth of the vector in a prokaryotic or eukaryotic host cell, extraction of the full-length antibodies from the culture medium or the cellular contents and purification of said antibodies.

38. (Withdrawn and Currently Amended) A method of obtaining monoclonal covalent antibodies, catalytic antibodies, covalent antibody fragments or catalytic antibody fragments from the lymphocytes of organisms with autoimmune disease, organisms with autoimmune disease, organisms without known disease or ~~transonic~~ transgenic mice expressing human antibody genes comprising the steps:

a) preparing a library of hybridoma cell lines, virus-transformed cell lines or immunoglobulin fragment genes cloned in and expressed from a vector.

b) screening and selecting ~~selection~~ for covalent activity of the antibodies or antibody fragments by binding to a[(n)] ~~antigenic~~ pCRA of claim 1 or a ~~polypeptide~~ or a protein;

c) screening and selecting ~~selection~~ for catalytic hydrolysis of a polypeptide or a protein by the antibodies or antibody fragments; and

d) purifying the antibodies or the antibody fragments.

39. (Canceled).

40. (Withdrawn and Currently Amended) The method of claim 38, wherein the antibodies or fragments thereof hydrolyze peptide bonds in superantigenic polypeptides.

41. (Withdrawn and Currently Amended) The method of claim 38, wherein the antibodies or fragments thereof hydrolyze gp120.

42. (Withdrawn and Currently Amended) The method of claim 38, wherein the antibodies or fragments thereof hydrolyze CD4.

43. (Withdrawn and Currently Amended) The method of claim 38, wherein the antibodies or fragments thereof hydrolyze beta-amyloid peptides.

44. (Canceled).

45. (Withdrawn) The method of claim 38, wherein the autoimmune disease is systemic lupus erythematosus.

46. (Withdrawn and Currently Amended) The method of claim 38, wherein the ~~immunoglobulin antibody~~ fragments are the VL and VH domains linked by a peptide linker.

47. (Withdrawn and Currently Amended) The method of claim 38, wherein the ~~immunoglobulin antibody~~ fragments are the light chain subunits.

48. (Withdrawn) The method of claim 38, wherein the vector is selected from the group consisting of phage display vectors, retroviral display vectors, yeast display vectors, bacterial display vectors and mammalian display vectors.

49. (Canceled).

50. (Withdrawn and Currently Amended) The method of claim 38, wherein the antibody fragments are single chain Fv fragments or light chains expressing covalent or catalytic activity isolated by steps comprising:

a) preparing the ~~immunoglobulin~~ antibody VL cDNA, VH cDNA and light chain cDNA by reverse-transcriptase polymerase chain reaction using as template the RNA from lymphocytes;

b) cloning the VL and VH cDNA in a form enabling their expression as single chain Fv fragments expressed on the surface of a display vector;

c) cloning the light chain cDNA in a vector in a form enabling their expression as single chain Fv fragments expressed on the surface of a display vector.

d) contacting the vector particles with immobilized pCRA of claim 1, removal of unbound vector particles by washing, and expressing the Fv cDNA or light chain cDNA from the pCRA-bound vector particles in a soluble form in prokaryotic or eukaryotic cells;

e) screening the soluble Fv or light chain constructs for covalent binding to the peptide or protein containing one or more antigenic determinants comprising the pCRA to isolate the covalent ~~antibody fragments antigen binding activity~~; and

f) screening the soluble Fv or light chain constructs for catalytic hydrolysis of a peptide or protein containing one or more antigenic determinants comprising the pCRA to isolate the catalytic antibody fragments ~~activity~~.

51. (Withdrawn and Currently Amended) Full-length lgG, lgM and lgA antibodies prepared from the Fv fragments of claim 50 ~~prepared~~ by steps comprising:

a) insertion of the VL and VH domain cDNA at the 5' side of lg constant domains contained in an expression vector by nucleic acid digestion and ligation procedures;

b) growth of the vectors in a prokaryotic or eukaryotic host cell, extraction of the full-length antibodies from the culture medium or the cellular contents and purification of said antibodies.

52. (Withdrawn and Currently Amended) Full-length lgG, lgM and lgA antibodies prepared from the light chain fragments of claims 50 ~~prepared~~ by steps comprising:

a) insertion of the light chain cDNA into an expression vector by nucleic acid digestion and ligation procedures;

b) insertion of the VH domain of gp120 binding antibodies at the 5' side of an lgG heavy chain constant domain contained in an expression vector by nucleic acid digestion and ligation procedures;

c) growth of the vectors in a prokaryotic or eukaryotic host cell, extraction of the full-length antibodies from the culture medium of the cellular contents and purification of said antibodies.

53. (Withdrawn. Currently Amended) The method of claim 38, wherein lymphocytes are obtained by steps comprising:

a) contacting the lymphocytes with a pCRA;

b) separating lymphocytes that are bound to the pCRA ~~from~~ from lymphocytes that are not bound to the pCRA.

54. (Canceled).

55. (Withdrawn) The method of claim 38, wherein the antibodies belong to the lgG, lgM, lgD, lgA or lgE classes.

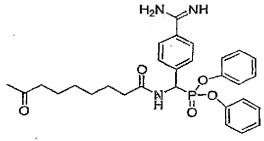
56. (Withdrawn and Currently Amended) The method of claim 38, wherein [$L_1 \ldots Lx \ldots Lm$] in the pCRA ~~represents an~~ comprises one or more antigenic determinants of a microbial protein, human, animal or plant peptide or protein or a cancer-associated peptide or protein.

57. (Withdrawn and Currently Amended) The method of claim 38, wherein [$L_1 \ldots Lx \ldots Lm$] in the pCRA ~~represents an~~ comprises one or more antigenic determinants of the HIV-1 protein [(.)]gp120, vasoactive intestinal peptide of epidermal growth factor.

58-61 (Canceled).

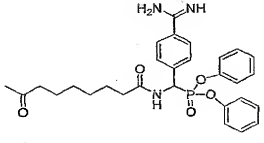
62. (Withdrawn) The method of claim 38 wherein n is from 1 to 23.

63. (Withdrawn) The method of claim 38, wherein the pCRA is gp120 derivatized at the Lys side chain amino groups at a density of 23 moles/mole protein with:

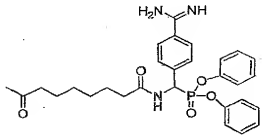


64. (Canceled).

65. (Withdrawn) The method of claim 38, wherein the pCRA is vasoactive intestinal peptide derivatized at the Lys20 side chain with:



66. (Withdrawn and Currently Amended) The method of claim 38, wherein the ~~immunogenic~~ antigenic determinant is derived from the soluble extra-cellular domain of the epidermal grouth factor receptor soluble extra-cellular domain CD4, Factor VIII, beta-amyloid peptide 1-40 or beta-amyloid peptide 1-42, each derivatized at Lys side chains with:



67. (Withdrawn and Currently Amended) A method to improve the covalent or catalytic activity of the antibody fragments of claim 12, comprising the steps:

a) introducing mutations of the VL and VH domains;

b) display of the resultant antibody fragments on the surface of a display vector;

c) contacting the vector particles with the pCRA[(W)], and removal of unbound vector particles;

d) screening the antibody fragments for covalent antigen binding activity;

e) screening the antibody fragments for catalytic activity.

68. (Canceled).

69. (Withdrawn and Currently Amended) A method for passive immunotherapy of a disease, comprising:

a) administering a therapeutically effective amount of antibodies having covalent or catalytic activity directed to ~~specific for~~ an antigen associated with a medical disorder in the patient, said antibody having been produced by the method of claim 1; and

b) repeating step a) as necessary for maintenance therapy.

70. (Withdrawn and Currently Amended) A method for passive immunotherapy of a disease, comprising:

a) administering a therapeutically effective amount of antibodies having covalent or catalytic activity directed to specific for an antigen associated with a medical disorder in the patient, said antibody having been produced by the method of claim 38; and

b) repeating step a) as necessary for maintenance therapy.

71. (Currently Amended) The method of claim 1, wherein the antibody or antibody fragment is directed to gp120 for immunotherapy of HIV-1 infection, hepatitis C virus protein E2 for immunotherapy of hepatitis infection, beta-amyloid peptide for immunotherapy of Alzheimer's disease, epidermal growth factor receptor for immunotherapy of cancer, or Factor VIII for immunotherapy of blood coagulation disorders.

72-75 (Canceled)

76. (Withdrawn and Currently Amended) A method for stimulating production of prophylactic antibodies in an organism, having covalent or catalytic activity directed to ~~specific for~~ an antigen associated with a medical condition in the organism, comprising the steps of:

a) administering to an organism a vaccine containing an immunogenic amount of a pCRA of claim 1 prepared from said antigen as of claim 1;

b) repeating step a) as necessary to ensure effective antibody production.

77. (Withdrawn) The method of claim 76, in which the medical disorder is a microbial disease and the pCRA is prepared from a constituent protein of the microbe.

78. (Withdrawn) The method of claim 77, in which the medical disorder is HIV-1 infection and the pCRA is prepared from gp120.

79. (Withdrawn and Currently Amended) A method of treating a medical disorder in a patient in inhibiting the action of an ~~catalytic~~ antibody, comprising the steps of:

a) administering to said patient a therapeutic amount of pCRA comprising one or more ~~in which the~~ antigenic determinants to which the antibody is directed ~~derived from an epitope irreversibly bound by said catalytic antibody~~;

b) assessing said patient for inactivation of said ~~catalytic~~ antibody; and

c) repeating step a) as necessary to maintain inhibition of said ~~action of said catalytic~~ antibody.

80. (Withdrawn and Currently Amended) The method of claim 79, wherein said medical disorder ~~disease state~~ is an autoimmune disease.

81. (Canceled).

82. (Withdrawn) The method of claim 79, wherein said medical disorder is a lymphoproliferative disorder.

83. (Withdrawn and Currently Amended) The method of claim 82, wherein said lymphoproliferative disorder is ~~selected from the group consisting of~~ multiple mycloma, acute lymphoblastic leukemia, lymphoblastic lymphoma, small lymphocytic lymphoma, lymphoplasmacytoid lymphoma, Waldenstroms macroglobulinemia, follicular center lymphoma, mucosa-associated lymphoid tissue lymphoma, hairy cell leukemia, diffuse large B-cell lymphoma, Burkitts lymphoma, or and node based monocytoid lymphoma.

84. (Withdrawn) The method of claim 12, wherein the organism expresses a genetic defect resulting in defective B cell receptor mediated transmembrane signaling in B cells.

85. (Withdrawn) The method of claim 84, in which the defective B cell receptor mediated transmembrane signaling is caused by altered expression of CD19, CD22 or Lyn.

86.-89. (Canceled)

90. (New) The method of claim 80 wherein said autoimmune disease is systemic lupus erythematosus, systemic scierosis, asthma, rheumatoid arthritis, mixed connective disease, Reiter's syndrome, Sjogren's syndrome, vasculitis, or bird shot retinopathy.